UNIVERSITY OF PITTSBURGH
GRADUATE SCHOOL OF PUBLIC HEALTH
PITTSBURGH, PENNSYLVANIA 15213

October 25, 1966

Grants and Research Contracts
Code SC
Office of Space Sciences
National Aeronautics and Space Administration
Washington, D.C. 20546

Dear Sir:

This is the eleventh quarterly progress report submitted in accordance with the requirements of NASA Contract NASr-169 covering the period 1 July through 30 September 1966.

Design drawings for the mechanized microscope were completed by the Perkin-Elmer group in mid-July and a design review carried out in the third week of July. Detailed drawings then were prepared of the individual sub-assemblies in the system. The need for certain clarifications to assure that the system solutions planned by the Perkin-Elmer group would suit the approaches planned here resulted in a meeting at the University with members of the Perkin-Elmer staff and our own group on September 13, 1966. The project status review carried out at that time was successful in that both groups were in accord in the details of the overall system.

Further work during this period at the University of Pittsburgh was devoted to the programming of the PDP 7 for control of the mechanized microscope and the development of necessary interface connections. Additional effort was also devoted to the construction of the amplifier components of the precision scanner system.

Our group was represented by one of us (N.W.) at three international meetings during this quarter. The first was a meeting of a study group on automatic karyotype analysis held at the headquarters of the International Atomic Energy Agency in Vienna, 21-23 June 1966. An internal report of the meeting, not intended for general circulation, is attached.

The second meeting was the Third International Congress of Radiation Research held at Cortina d'Ampezzo, Italy, from June 26 to July 2, 1966. The third was the Third International Congress of Human Genetics held in Chicago, Illinois September 5 to 10, 1966. Abstracts of the material presented at the second and third of these meetings is attached.

Other significant developments in the project include a relocation of the work. Several considerations, including the increasing quantity of hardware developing in this project made it necessary to move from our research laboratory in Children's Hospital to a suite of rooms on the 11th floor of Presbyterian-University Hospital, an adjoining building. The physical facilities here are better suited to our work.

Respectfully Submitted,

Niel Wald

Niel Wald, M.D.
Professor of Radiation Health

THIRD INTERNATIONAL CONGRESS OF HUMAN GENETICS

CHICAGO, SEPTEMBER 5-10, 1966

ABSTRACTS OF CONTRIBUTED PAPERS

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thought that there was in Polynesian races. Hawaiians (Stewart, the incidence in Maori 00 which was approxi- in Europeans living in es (1964) studied the es of European index Falconer (1965) used of heretability of club ations. Since club foot various estimates were ex only compared with ases. The various esti- ed were all consistent with each other and a weighted mean gave a value of 70% (S.E.8).

The present investigation is based on the incidence of club foot among the first, second and third degree relatives of Maori index cases with talipes equinovarus. These estimates all agree with one another and so the concept of an underlying variable "liability to club foot" with a fixed threshold above which all persons are affected is probably correct. Heritability was found to be high so that genetic factors are of prime importance in causing club foot.

Intrauterine environmental factors have long been thought to be important in the etiology of club foot and the Maori families have been analysed in such a way as to throw some light on this question.

337. Vogen, F., University of Heidelberg, Heidelberg, Germany. *Chemical mutagenesis: an outline of a research program and examinations in primary populations.* ABSTRACT NOT RECEIVED.

338. Wald, N., Feagin, F. E., and Ranshaw, R. W., University of Pittsburgh, Pittsburgh, Pa. *The automation of cytogenetic analysis: a progress report.*

Contemporary manual cytogenetic techniques have been used satisfactorily in our laboratory for clinical diagnostic research and to investigate rodent leukemogenesis related to environmental agents. In the measurement of karyotype variability in a newborn population, and the cytogenetic monitoring of an occupationally radiation-exposed population, the procedures were less satisfactory. A major limiting factor for detailed quantitative studies of this type on a large scale is the slow, complex and tedious nature of the techniques. We have therefore undertaken to automate the process from the scanning of prepared microscope slides to locate mitotic cells through the determination of the modal chromosome count and the recognition of any morphologically atypical chromosomes in the karyotypes. An automatic microscope, developed in collaboration with the Perkin-Elmer Corporation, uses a coherent monoenergetic laser light source to scan the slides, recognizes mitotic cells by their optical Fourier transforms, and transmits the images to film or directly to a differential amplifier via a precision flying spot scanner. Filmed images may also be introduced by a mechanical or an electronic scanner. The resultant signal is converted from analog to digital form, stored in magnetic memory and recorded on magnetic tape. The output is analyzed by a computer pattern-recognition program developed for chromosome counting and karyotyping. The details of current progress will be presented.

This work is supported by funds provided under National Aeronautics and Space Administration Contract NASR-169. Computer work has been partially supported by National Science Foundation G-11039.

339. Walker, F. A., and DeMars, R., University of Wisconsin, Madison, Wis. *Enzyme alterations in fibroblasts derived from patients with Down's syndrome.*

It has been shown that the neutrophile leukocytes in patients with Down's Syndrome are abnormal both histologically and biochemically. However, studies have suggested that there may be biochemical differences in fibroblasts in tissue culture associated with aneuploidy for a small acrocentric chromosome.

Initial studies of 8 normal and 8 trisomic cell strains derived from skin biopsies showed no difference during the log phase of growth between the control and trisomic cultures when assayed for alkaline phosphatase at pH 9.2 in glycine buffer, acid phosphatase at pH 5.3 in acetate buffer, both with 3×10^{-4}M paranitrophenol phosphate as substrate. Similarly, β-glucronidase activity showed no significant differences between strains. However, the average gamma-glutamyl transferase activity was increased in the trisomic strains when compared with the normal controls.

A method was developed for quantitating the histochemical alkaline phosphatase assay described by Burstone using a spectrophotometric assay of the dye eluted from cell monolayers. Preliminary results show a diphasic distribution of the alkaline phosphatase activity at pH 8.6 in Tris buffer with Napthol ASMX phosphate as substrate in control strains and that all the strains derived from patients with Down's Syndrome (Trisomy 22) showed increased activity. There was no correlation between alkaline phosphatase activity at pH 9.2 with paranitriphenol phosphate as subtrate during the long phase of growth.

This work was supported by the National Institutes of Health (Grants #GM-08217 and #GM-06983).

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THIRD INTERNATIONAL CONGRESS OF RADIATION RESEARCH

B O O K O F A B S T R A C T S

Cortina D'Ampezzo

June 26 - July 2, 1966

925 69

AUTOMATED CHROMOSOME ANALYSIS IN RADIOBIOLOGIC RESEARCH AND MONITORING

N. WALD, F. E. FEAGIN and R. W. RANSHAW
N. W. and F. E. F.: Graduate School of Public Health, University of Pittsburgh - R. W. R.: Computation and Data Processing Center, University of Pittsburgh, Pittsburgh, Pennsylvania, 15213, U. S. A.

Contemporary manual cytogenetic techniques have been used in our laboratory to investigate the mechanism and dose response relationship between radiation and the production of mammalian blood cell chromosomal aberrations. The relationship between such aberrations and the occurrence of the blood dyscrasia, leukemia, has also been examined. In addition, the feasibility of utilizing blood chromosome analyses for the biologic monitoring of occupationally radiation-exposed human populations has been considered. A major limiting factor for detailed quantitative studies of this type on a large scale is the slow, complex and tedious nature of the techniques. We have therefore undertaken to automate the process from the scanning of prepared microscope slides to locate mitotic cells through the determination of the modal chromosome count and the recognition of any morphologically atypical chromosomes in the karyotypes. An automatic microscope, developed in collaboration with the Perkin-Elmer Corporation, uses a coherent monoenergetic laser light source to scan the slides, recognizes mitotic cells by their optical Fourier transforms, and transmits the images to film or directly to a differential amplifier via a precision flying spot scanner. Filmed images may also be introduced by a mechanical or an electronic scanner. The resultant signal is converted from analog to digital form, stored in magnetic memory and recorded on magnetic tape. The output is analyzed by a computer pattern-recognition program developed for chromosome counting and karyotyping. The details of current progress will be presented.

This work is supported by funds provided under National Aeronautics and Space Administration Contract NASr-169. Computer work has been partially supported by National Science Foundation grant G-11039.

926 9

AGING IN IRRADIATED AND UNIRRADIATED GERMFREE MICE*

H. E. WALBURG, JR. AND G. E. COSGROVE
Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee, U.S.A.

The life span and incidence of diseases have been studied in unirradiated and x-irradiated (300 R at 5 to 6 weeks of age) conventional and germfree RFM/Un and ICR mice. Preliminary data suggest that the mortality rate is lower in both irradiated and unirradiated germfree mice than their conventional counterparts over the first 2/3 of the life span and that such differences tend to diminish and may disappear in the last 1/3 of life. The germfree mice of both strains have resembled the conventional mice in the development of lymphatic leukemia, reticulum cell sarcoma, and solid tumors of various sites; however, they have failed to develop myeloid leukemia, which is a characteristic radiation response of the conventional RFM mouse. Both irradiated and unirradiated germfree mice have shown glomerulosclerosis, although the incidence and severity of the disease appear to be lower than in the conventional mice. Miscellaneous lesions (i.e., arteriosclerosis, amyloidosis, auricular thrombosis, pyelonephritis, and polyarteritis) have been seen in the germfree, as well as the conventional, mice of both strains, but inflammatory lesions associated with infectious microorganisms (such as otitis media, abscesses, and ulcerative dermatitis) have been seen only in the conventional mice. Cecal volvulus, apparently associated with the large cecum of germfree mice, has been noted only in the germfree ICR mice. The general similarity of widely diverse pathological lesions between germfree and conventional mice suggests that the absence of a detectable microbial flora and fauna alters aging processes and late somatic effects of radiation relatively little. However, a few notable exceptions have been observed, one being the absence of myeloid leukemia in germfree mice. These exceptions warrant further study.

*Research sponsored by the U.S. Atomic Energy Commission under contract with the Union Carbide Corporation.

927 64

INDUCED MUTATIONS AT SPECIFIC LOCI IN HIGHER PLANTS. II. MULTIPLE ALLELES AT THE Vb LOCUS IN AVENA BYZANTINA C. KOCH.

A. T. WALLACE
University of Florida, Gainesville, Florida, U. S. A.

The Vb locus (or closely linked multiple loci) in Avena byzantina controls the reaction(s) to the two pathogens, Helminthosporium victoriae M & M, a facultative parasite, and Puccinia coronata var. avenae CDA, an obligate parasite. The dominant wild type allele (Vb) provides both susceptibility to H. victoriae (and its toxin) and resistance to P. coronata and vice versa. Seed stocks from 175 independently induced mutants expressing full resistance and 40 expressing partial resistance to H. victoriae toxin (produced by both ionizing radiations and mutagenic chemicals) have been isolated and purified and are being investigated. Genetic analysis of F_2 data from 450 crosses involving 69 full-resistant and two partially resistant mutants indicate that all are located at the same locus. These F_2 data along with other data from a classification of the mutants indicate that there is an inverse relationship between the degree of toxin resistance and dominance, that only part of the locus influences sensitivity to P. coronata races, that this portion of the locus controls the loss of electrolytes from toxin-treated cells and the increased respiration of toxin treated tissue. The entire locus appears to be involved in the toxin resistance-susceptibility relationship. The data suggests that a constitutive "receptor" in the toxin-susceptible wild type mutants and the activity of the "recepter" in certain, but not all, of the partial resistant mutants is modifiable by changes in temperature.

928 60

A MARKOV TREATMENT OF ENERGY TRANSFER LEADING TO LUMINESCENCE IN EXCITED POLYMETHYL METHACRYLATE CONTAINING p-TERPHENYL*

D. WARD, D. G. GARDNER and J. C. GARDNER
D. W. and D. G. G.: Chemistry Dept., Illinois Institute of Technology, Chicago, Illinois - J. C. G.: Mathematics Dept., California State College, Hayward, California.

A study has been made of the luminescence from excited samples of predominently syndiotactic polymethyl methacrylate (PMMA) which contained the scintillator p-terphenyl, and which contained in some cases an additional nonluminescent energy sink either in solid solution or attached directly to the polymer chain. In the latter case a copolymer of a few percent α-methyl styrene was used, while in the former case cumene was added in solid solution. In some experiments light in the range 2200-3200 A. was used to excite the samples, while in other experiments conversion electrons from the radioactive isotope Cs-137 were used. In the ultraviolet light work absolute quantum efficiencies for luminescence were obtained. Energy is presumed to migrate in these systems as excited molecular states and ions. A Markov chain treatment of this migration yielded equations predicting the quantum efficiency for luminescence and for chain scission in optically excited systems not containing the additional energy sink. The luminescence results are in excellent agreement with the general form of the derived equations, and in addition could be used to accurately predict the chain scission results. The results from the electron experiments appear to indicate that energy transport by positive ions over short distances may be an important mechanism. A preliminary treatment of the time dependence of the luminescence has also been made.

* Supported in part by the U. S. Atomic Energy Commission.

Professor N. Wald

INTERNATIONAL ATOMIC ENERGY AGENCY

INTEROFFICE MEMORANDUM

TO: All Study Group Participants

FROM: M. W. Miller Morton W. Miller

SUBJECT: Report of the Discussions Held at the Study Group Meeting on Karyotype Analysis, 21 - 23 June 1966

Enclosed is the final draft of the Study Group Meeting discussions on karyotyping automatically. This report is strictly for internal/"house" distribution and will not in any way be published.

Thanks again for your interest - should you be in Vienna at any time and have a few moments to spare do not hesitate to stop by.

REPORT

DISCUSSIONS AT THE STUDY GROUP MEETING ON AUTOMATION OF KARYOTYPE ANALYSIS

A Study Group Meeting was convened at the Vienna Headquarters of the International Atomic Energy Agency from 21 - 23 June 1966, to consider the current status of the automation of karyotype analysis. There were eleven invited participants working in various but related aspects of the problem of karyotyping automatically. The moderator was Dr. H. D. Bruner (Division of Biology and Medicine, USAEC) and the scientific secretary was Dr. M. W. Miller (IAEA, Vienna).

A view of where we stand on karyotyping was the subject of the opening talk by Dr. Bruner, who emphasized the possibility of karyotyping as a means of evaluating damage in an individual; he also recognized the legal implication of equating radiation damage with chromosome anomalies.

Dr. Patricia Jacobs (UK) spoke on the biological aspect of the automation of karyotype analysis and listed the parameters used in describing chromosomes -- e.g. mass, length and position of the centromere - and the various types of chromosome anomalies that are scored in karyotyping. Chromosome anomalies fall into two general categories. First, there are those abnormalities which are relatively "easy" to score as the same abnormality occurs in all, or a large number of cells from an affected individual. Secondly, there are those abnormalities induced by various environmental agents such as irradiation, chemicals and viruses which are "difficult" to score as there is no consistency in pattern of the chomosomes of the abnormal cells. The abnormal cells may contain structurally abnormal chromosomes such as dicentrics, acentric fragments or deletions, and cells carrying such abnormalities may be common in the sample or they may be infrequent, and in the latter case, a large number of cells have to be analysed to give reliable results.

A machine that can automatically detect and locate metaphase spreads on microscope slides was described by Dr. Kendall Preston (Perkin-Elmer Corp. USA); this machine employs a coherent beam from a gas laser and will scan one thousand 50 sq. micra fields per seconds this work was done for the University of Pittsburgh under the auspices of a contract from the National Aeronautics and Space Administration. The configuration of metaphase chromosomes diffracts the coherent light at specific angles and by the appropriate placement of detectors the signal can be separated from others. The co-ordinates of location of the metaphase on the slide are also determined. A "flying-spot" also gives pulses which, when the beam traverses a metaphase, differ from those due to cell nuclei but, as with the gas laser beam, does not differentiate "good" from "bad" spreads although the machine never ends a stop on a non-dividing cell. In its present form, the device had difficulty in distinguishing artefacts (in particular surface dust and other contamination). In another experiment using a flying-spot scanner to examine metaphase spreads, it was found that measurements of the pulse output spectrum were not able to differentiate "good" from "bad" spreads but was able to determine the optimum focal plane for both viewing and photography. Dr. Preston felt that automation of any step or portion of the total procedure is desirable and should be made.

A computer programme for karyotype analysis starting from measurements of the arm lengths of the chromosomes was the subject of a talk by Dr. C.W. Gilbert (UK). This programme begins with the premise that the majority of the chromosomes are paired. A quadratic "difference measure", based on arm lengths is used and the 150 smallest values from all possible pairs selected and from them an acceptance limit established for use in the analysis. The method then examines and assigns acceptable pairs within groups of chromosomes in comparison with an established normal set of values for each chromosome type. Any unpaired chromosomes are allocated to the nearest acceptable normal type or classified as unrecognisable. Examples of successful analysis of human karyotypes were shown.

Dr. Preston described problems relating to high speed counting and sizing employing both slits and flying-spot scanners. A computer logic was presented which would permit the single-scan counting of arrays of arbitrarily

shaped chromosome-like objects in a field of view using the "area continuity" method. The SHRINK algorithm was described which is currently being used in the CELLSCAN™ system. These methods have potential application in directly scanning, counting and determining the topography of non-overlapping chromosomes.

Dr. L. Kamentsky (IBM Watson Lab. USA) referred to his present work on detection of PAP test cells for uterine cancer as an example of alternative ways of approaching the problem of karyotyping. He pointed out that karyotyping might be accomplished by methods other than simulating the way the eye and brane behave. In the case of the PAP cells, his group has devised a machine to scan cells by lead and/or tungster spot beams so as to obtain estimates of DNA and RNA per cell. The very high speed of analysis of each cell and the large numbers of cells screened can give data which statistically may be as meaningful as the manually accomplished high precision examination of individual cells. A fast system detecting some special quality of a dividing cell might be developed to separate them as they flow through a channel and so concentrate them for any other type of subsequent analysis.

Dr. N. Wald (USA) spoke about various agents in addition to ionizing radiation which are known to produce chromosome abnormalities, and he emphasised the current assumption that a chromosome change is an index of an environmental effect. The importance of this point to human health lies in the possibility of recognizing biological changes before they reach the stage of biological disease. A system is being built which combines Preston's method for scanning with a laser beam and a flying-spot microscope scanner. Eventually, these apparatuses will be used to study some of the environmental factors as they may relate to chromosome anomalies.

Dr. Denis Rutovitz (UK) described one approach to the problem of identifying chromosomes from photographs using seven grey levels as obtained by a FIDAC system. He discussed some of the limitations of this system, particularly those of inadequate rendering of grayness and reviewed a variety of methods of abstracting and identifying a chromosome and its major morphological features. It was felt that no one method of logic would work for the identification of all chromosomes although the more complex systems should be

reserved for those instances not susceptible to the simpler or routine procedures. He suggested that as a last resort, the chromosome could be presented to an operator of a screen console for manual identification. Dr. P. Jacobs classified chromosomes into "easy", "moderate" and "unmanageable" categories on the basis of Dr. Rutovitz' assessment of the qualities important to machine perception: they found that about 50% of the chromosomes in conventionally usable cells were classified as "easy" on machine tests, approximately 30% as "moderate", 16% as "unmanageable" and 2-7% as "unmanageable". According to these criteria, operator intervention would be required at least once for every metaphase for complete analysis of individual cells. An alternative would be to build up composite karyotypes for an individual by combining the results of partial analysis of a member of different cells.

CYDAC, a high-fidelity, photometrically oriented scanning system is being applied to the chromosome problem by Dr. M. L. Mendelsohn and colleagues (USA). This device produces forty-thousand equally spaced 8-bit optical density readings in a 50 by 50 micron area of a microscope slide. A computer is used to evaluate the digital images obtained by the scanner. One orientation of this group is toward the development of appropriate parameters to extend machine perception. For example, they have successfully used DNA content as a parameter for chromosome analysis. Eventually, it is hoped that further automation and the application of several parameters in parallel will match or exceed the quality of visual chromosome analysis.

Dr. Le Go (France) described the karyotyping and hematologic changes found in Mr. Jensen, the man accidentally exposed to a criticality at Mol: the dose to the foot (10% neutrons and 90% gamma rays) was computed by phantoms to be 4500 rads, the dose to the top of the head 300 rads, with the rest of the body scaling in between. The minimal values were: polycytes - $40/mm^3$ on day 25; lymphocytes - $130/mm^3$ on about day 4; platelets - $14\text{-}16,000/mm^3$ from days 21 - 26. The chromosome abnormalities seen on day 2 consisted of polyploidy, breakage and dicentrics. The low number of lymphocytes makes statements of percentages of frequencies rather difficult. Dr. Jacobs felt that the polyploidy was an effect of the cells having tried to go into second or even third division while still in the three days of culture. The complexity of metaphases on this patient would be a challenge to a computer if presently available.

Dr. C. Favier (France) discussed the statistical properties of length ratios in the context of karyotype analysis. A Chi-square index was developed combining the total length and arm ratio as well as a two dimensional graphical display of those two parameters.

Dr. L. Kertész (Hungary) commented on the way machine karyotype analysis would be helpful for the biological research and health studies and also mentioned that "manual" parts of this kind of research are currently being undertaken in Hungary. He felt that the Agency should organize a training course for radiologists and radiation health physicians who, by profession, are in a position to screen a relatively large population exposed to high radiation doses.

After the technical diversity of the detailed presentations, general discussion revealed a remarkable consensus among the panel members with regard to recommendations and the overall status of the field. Over a dozen laboratories are currently committed to programmes involving machine analysis of visually oriented chromosome spreads. Within this area, there is a healthy diversity of approaches but hopefully research on the automation of chromosomal data will eventually spread beyond the confines of classical visually oriented methods. Following Dr. Kamentsky's example, the possibility of using flow systems to isolate individual chromosomes was discussed as well as other potential methods to measure the incidence of gross observations without necessarily performing individual karyotypes. It was also recognized that parts of the karyotype procedure other than image analysis of the chromosomes will have to be developed. These include standard and automatic methods of preparation of stained metaphase cells, searching for suitable metaphases, formal identification procedures, correlation with phenotype (or medical records, family history or occupational exposures, etc.) and accumulation of archives of genetic data.

The Study Group viewed several successive stages in the development of the field and tabulated a set of goals which were indicated as "immediate", "long range" and "long-long-range". First is a semi-automatic approach to automation in which a human operator works closely with the machine. One example of this would be a device that takes length measurements under the supervision of an

operator. In one form of this approach, the operator points to chromosomes or identifies centromeres using a light pen. The "immediate" goal is a clear effort at standardizing sample preparation methods, terminology, etc. in addition ot its achieving semi-automatic "assists" to the karyotyper.

The next level of sophistication in terms on "long range" goals would be a system capable of a fully automated analysis of "easy" metaphases such as those which occur with congenital defects. When perplexed by a difficult image, this system would refer to an operator for help. In this case the operator would interact with the machine sporadically and only in terms of a particular problem the machine presented to him. In the final stage of sophistication, one would have a completely automatic device. This "long-long-range" goal concerns also the development of completely new methods and measurements for determining genetic normality/abnormality and the full automation of the mitotic cell analysis including the culturing of cells as well as the generation of the karyotype. It was also recognized that full automation might well be such a complex task that it would be uneconomic to realize.

There is no certainty at present as to which levels are feasible, economical or realistic. Thus, it is recommended to have systems at several levels being developed in parallel in different laboratories, and hopefully, information will soon be available on the merits of competing systems.

It was clear to all that some form of automation is essential if progress is to be made in a wide variety of important problems in human genetics.

1. Screening of newborns to establish levels for various human human popilations
2. Screening of adults
3. Study of special groups, such as mental defectives, criminals, etc.
4. Effect(s) of age
5. Effect(s) of environmental hazard, including drugs, radiation and industrial chemicals

6. Medical applications

7. Basic Research in human genetics

8. Study of biological systems other than man

It remains to be seen how soon, in what form, and to what extent machines will assist man in achieving these ends. Furthermore, it must be established to what extent karyotype analysis per se is a valid procedure in terms of the biological, preparative and statistical variables involved.

In a brief discussion of the Agency's possible role in the subject, the panel felt that a continued support of basic chromosome research was reasonable. Sponsorship of a future meeting was considered and there was a general consensus that a meeting in perhaps 18 months' time would be appropriate.